Docket No. T2315-907789

#11
1 of 3
JRP
6/5/03

**IN THE UNITED STATES PATENT & TRADEMARK OFFICE**
**BEFORE THE BOARD OF PATENT APPEALS & INTERFERENCES**

Appellant: Raymond J. BERGERON, JR. :

Serial No.: 10/091,591 : Art Unit: 1614

Filed: March 27, 2002 : Examiner: Rebecca Cook

For: Method and Composition for the Treatment of Diarrhea and Gastrointestinal Spasms :

**BRIEF ON APPEAL**

Mail Stop Appeal Brief-Patents
Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

Sir:

The following Brief on Appeal is submitted in support of the appeal of the Office Action mailed April 11, 2003, wherein the Examiner finally rejected claims 1-7.

The appeal fee of $ 160.00 is submitted herewith.

To the extent necessary, appellant petitions for an extension of time under 37 CFR §1.136. Please charge any additional fees due (or credit any overpayment thereof) to Deposit Account No. 50-1165 (Docket No. T2315-907789).

Respectfully submitted,

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Filed: May 28, 2003

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## TABLE OF AUTHORITIES

## REAL PARTY IN INTEREST

The real party in interest herein is the University of Florida, to which the above-captioned application is assigned by virtue of an Assignment from the inventor executed May 20, 2002, which was recorded August 11, 1995, on Reel 012952 at Frame 0256.

## RELATED APPEALS AND INTERFERENCES

The invention described in the claims on appeal herein is related to none described in any other U.S. patent application on appeal to the U.S. Patent & Trademark Office Board of patent Appeals and Interferences known to appellant.

## STATUS OF CLAIMS

The above-captioned application was filed with original claims 1-14. Claims 8-14 were cancelled in the Preliminary Amendment filed with the application. This is an appeal from the final rejection of claims 1-7, all of the claims remaining in the application.

## STATUS OF AMENDMENTS

No amendments have been filed subsequent to the final Office Action, Paper No.8, mailed April 11, 2003.

## SUMMARY OF THE INVENTION

The present invention relates to anti-diarrheal, anti-secretory, or gastrointestinal anti-spasmodic pharmaceutical compositions comprising an anti-diarrheal or gastrointestinal antispasmodic (hereinafter "GI anti-spasmodic") effective amount of a polyamine of the formula set forth below and a pharmaceutically acceptable carrier therefore:

$$R_1\text{-}N^1(R_2)\text{-}(CH_2)x\text{-}N^2H\text{-}Q\text{-}N^3H\text{-}(CH_2)y\text{-}N^4(R_3)\text{-}R_4\text{----------(I)}$$

wherein: $R_1$, $R_2$, $R_3$ and $R_4$ may be the same or different and are H, alkyl, cycloalkyl or aralkyl having from 1 to 12 carbon atoms, or a heterocyclic group having from 3 to 10 atoms wherein the hetero atom is said $N^1$ or $N^4$ ;

Q is a cycloalkyl group having from 3 to 10 carbon atoms;

x is an integer from 3 to 6, inclusive;

and y is an integer from 3 to 6, inclusive;

or (II) a salt thereof with a pharmaceutically acceptable acid.

The present invention is predicated on the discovery that polyamines of the above formula act to inhibit the potential for the large and small intestines to contract. While not wishing to be bound by any theory as to the mechanism of action of the polyamines as inhibitors of this action of the intestines, it is hypothesized that the polyamines function via a receptor-dependent regulation mechanism whereby the myoelectric activity of the muscle tissue of the colon and small intestine and the secretion of fluid and electrolytes by these organs are modulated. In addition, some of these above effects may be directly or indirectly mediated through the release of nitric oxide or through the activation of nitric oxide synthase.

## ISSUES ON APPEAL

Claims 1-7 stand finally rejected under 35 USC §102(b) as anticipated by U.S. 5,962,533 and CA124:25633.

An issue presented for appeal is whether the invention as claimed in claims 1-7 is completely anticipated by each of the above references within the meaning of 35 USC §102(b).

## GROUPING OF CLAIMS

The appealed claims stand or fall together.

## ARGUMENTS

The claims stand rejected in the Final Office Action as "anticipated (35 USC §102(b)) by 5,962,533 and CA124:25633 for the reason given in Paper No. 5". In Paper No. 5 the "reason" is stated as: "The references disclose compositions comprising the instant compound and that it is used to treat diarrhea".

Prior to setting forth arguments against the stated ground of rejection, appellant notes the following:

First, the stated ground of rejection is based upon 35 USC §102(b). Thus the Examiner is obliged to show that each element set forth in each rejected claim is specifically disclosed by each of the references relied upon. See *In re Brown, 141 USPQ 166.* Appellant will demonstrate that the Examiner has not and, indeed, cannot carry this burden. In doing so, appellant will set forth a variety of arguments, none of which should be construed as arguments that the claimed compositions are "unobvious" over the cited references, as that term is employed in 35 USC §103. The stated ground of rejection is 35 USC §102(b) and not 35 USC §103. It is well settled that, on appeal to the U.S. Patent & Trademark Office Board of Patent Appeals & Interferences (hereinafter, "Board"), neither the Examiner nor the Board

has license to shift the statutory basis of a rejection from Section 102 to 103 since to do so would deny appellant the procedural due process provided by 37 CFR 196(b). See *In re Meyer, 202 USPQ 175; In re Hughes, 145 USPQ 467 and In re Echard, 176 USPQ 321.* Nothing set forth in the arguments presented below should be construed as a waiver by appellant of the above-noted "procedural due process" guaranteed by 37 CFR 196(b).

Secondly, it is noted that the Examiner relies upon the reference identified as "CA124:25633". This reference is an abstract of a *J. Med. Chem.* [1996, v. 39, pp. 2461-2471] article in Chemical Abstracts. In the interests of fully disposing of this ground of rejection, appellant herein proposes, with the Examiner's and the Board's permission, to substitute the original article for the abstract thereof since the former is obviously the "best reference" of the two. A copy of the original article is attached hereto as Exhibit A.

**US 5,962,533**

The patent discloses (paragraph bridging cols. 4 & 5; col. 17, lines 27-59) and claims (claim 5) pharmaceutical compositions for the treatment of diarrhea comprising a polyamine and a pharmaceutically acceptable carrier wherein the polyamine has the formula:

> *"---H-$N^1(R_1)$-$ALK_1$-$N^2(R_2)$-$ALK_2$-$N^3(R_3)$-$ALK_3$-$N^4(R_4)$-H or its possible stereoisomers or a salt thereof with a pharmaceutically acceptable acid wherein:*
>
> *$R_1$ and $R_4$ may be the same or different and are alkyl, aryl, aryl alkyl or cycloalkyl, optionally having an alkyl chain interrupted by at least one etheric oxygen atom;*
>
> *$R_2$ and $R_3$ may be the same or different and are $R_1$, $R_4$ or H;*
>
> *$N^1$, $N^2$, $N^3$ and $N^4$ are nitrogen atoms capable of protonation at physiological pH's;*
>
> *$ALK_1$, $ALK_2$ and $ALK_3$ may be the same or different and are straight or branched chain alkylene bridging groups having 1 to 4 carbon atoms which effectively maintain the distance between the nitrogen atoms such that the polyamine:*

*(i) is capable of uptake by a target cell upon administration of the polyamine to a human or non-human animal or is capable of binding to at least one polyamine site of a receptor located within or on the surface of a cell upon administration of the polyamine to a human or non-human animal; and*

*(ii) upon uptake by the target cell, competitively binds via an electrostatic interaction between the positively charged nitrogen atoms to biological counter-anions;*

*the polyamine, upon binding to the biological counter-anion in the cell, functions in a manner biologically different than the intracellular polyamines; and*

*further wherein at least one of said bridging groups $ALK_1$, $ALK_2$ and $ALK_3$ contains at least one --CH(OH)-- group which is not alpha- to either of the nitrogen atoms.---"* (emphasis added)

It is critical to appellant's position herein that it be recognized that the only polyamines disclosed by the patent (other than those disclosed in col. 17, lines 27-59) to be effective anti-diarrheals are those of the above formula which contain at least one CH(OH) group in at least one of the bridging groups. The only pharmaceutical compositions for the treatment of diarrhea disclosed or claimed by the patent are those containing a polyamine of the above formula which contains at least one CH(OH) group in at least one of the bridging groups.

Appellant is not claiming a pharmaceutical composition for the treatment of diarrhea containing a polyamine which contains at least one CH(OH) group in at least one of the bridging groups. Rather, the claims are drawn to pharmaceutical compositions for the treatment of diarrhea containing a polyamine wherein $ALK_1$ and $ALK_3$ are certain alkyl groups and $ALK_2$ is a cycloalkyl group having 3 to 10 carbon atoms and none of the bridging groups contain CH(OH) groups.

The basis for the Examiner's rejection is that the patent discloses, in table 1, two polyamines (compounds 33 and 34) that fall within the structural formulae of the rejected claims. There is no question but that compounds 33 and 34 are embraced by the structural formulae of the rejected claims. However, there is no disclosure in the reference that

compounds 33 and 34 are anti-diarrheals. There is no disclosure in the reference of a pharmaceutical composition suitable for the treatment of diarrhea that contains either compound 33 or 34. Accordingly, there is no basis for rejecting the present claims over this patent reference under 35 USC §102.

Certainly, the mere inclusion of compounds 33 and 34 in Table 1 does not constitute an anticipation of the claims under 35 USC §102. Table 1 of the patent sets forth the calculated and actual $K_i$ values for a wide variety of polyamines. The table was compiled by patentee as a first step in trying to predict which polyamines would be effective anti-diarrheals. See col. 6, lines 25-60. Table 1,described as "library of compounds" (col. 6, lines 53-54) includes 34 compounds and, as stated above, merely delineates the $K_i$ values for the listed polyamines.

At cols. 11 and 12 (the disclosure between the two tables) it is disclosed that the compounds listed in Table 1 would require further testing to determine whether they would be good candidates for use as antidiarrheals. The fact that neither of compounds 33 or 34 are mentioned again in the subsequent disclosure of the patent, after their appearance in the Table 1 "library", as even potential anti-diarrheals is conclusive evidence that the reference cannot be said to anticipate the claimed invention within the meaning of 35 USC §102.

If one follows the Examiner's reasoning to its logical conclusion, every "compound" mentioned in the patent (and, it is important to bear in mind, compounds 33 and 34 are only "mentioned" in Table 1) would have the requisite properties to render it useful for the treatment of any condition "mentioned" in the patent. The absurdity of this conclusion further points up the invalidity of the stated ground of rejection.

That Table 1 is merely a first step in the "computer modeling" program described in col. 6 of the patent for "designing" potential candidates for anti-diarrheal therapy is apparent from the fact that none of the compounds in the "library" of Table 1 are embraced by the

claims of that patent. It is clear from an examination of the reference that the Examiner has somehow misinterpreted Table 1 as disclosing "compositions for the treatment of diarrhea" containing the polyamines listed therein. If this is the Examiner's position, it is respectfully requested that the Examiner specify those portions of Table 1 or any other part of the disclosure that identify compounds 33 and 34 as anti-diarrheals and their inclusion in pharmaceutical compositions for the treatment of diarrhea.

**The CA reference**

The original *J. Med. Chem.* Article abstracted in the CA reference contains a disclosure virtually identical to that of the 5,962,533 patent reference.

Thus, Table 1 of the Journal article is identical to Table 1 of the patent. The right-hand column of page 2463 describes in detail the "computer modeling" technique for designing potential anti-diarrheal polyamines for which Table 1 comprises a first step.

Most importantly, however, the Journal article points up the difficulty in determining a polyamine's anti-diarrheal activity. In the disclosure in the right=hand column of page 2461, it is disclosed:

> *"---In a series of elegant experiments, Tansy was able to demonstrate that polyamines have a pronounced effect on the motility of the GI tract---It soon became clear that polyamines had a profound influence on gastric emptying and that---from a structure-activity perspective it also became obvious that very small changes in the polyamine's structure could completely eradicate the molecule's ability to inhibit gastric emptying---"* (emphasis added).

Obviously, therefore, the authors of the article did not envision that all of the polyamines listed in Table 1 would operate as anti-diarrheals. It is clear that the table was merely the first step in designing a suitable anti-diarrheal by computer modeling and that it represents only a library of suitable candidates for tailoring to achieve this effect.

Note also the disclosure in the left-hand column of page 2462:

> *"---The current study is aimed at the design, synthesis and testing of an anti-diarrheal (polyamine) derivative---i.e., a metabolically programmed drug---"*

Given the stated objective of the authors, it is only the CH(OH) group containing polyamines that are identified as anti-diarrheals. Is it logical to conclude that they would overlook two of the polyamines listed in Table 1 as anti-diarrheals? Of course not; the polyamines of Table 1 are listed merely to construct a "library" from which to initiate the computer modeling technique described in the article.

**US Patent 6,399,662**

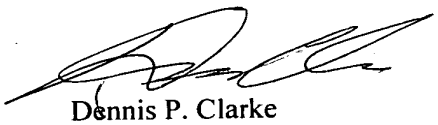
Attention is drawn to the recent issuance of US patent no. 6,399,662. That patent contains claims drawn to methods of treating diarrhea by administering to patients in need thereof the same polyamines described in the present claims and issued in spite of the fact that US patent no. 5,962,533, one of the references relied upon by the Examiner herein, was cited thereagainst. It is respectfully submitted that it would be highly contradictory in light of this fact to affirm the present rejection.

## CONCLUSION

It is clear that the Examiner has not demonstrated that either of the references relied upon disclose the claimed pharmaceutical compositions. Accordingly, it is respectfully requested that the final rejection of record be reversed and the application remanded to the Examiner for immediate allowance.

Respectfully submitted,

MILES & STOCKBRIDGE



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## APPENDIX OF CLAIMS ON APPEAL – SERIAL NO. 10/091,591

**Claims 1-7**

1. An anti-diarrheal or gastrointestinal anti-spasmodic pharmaceutical composition comprising [A] an effective amount of a compound having the formula:

$$R_1\text{-}N^1(R_2)\text{-}(CH_2)x\text{-}N^2H\text{-}Q\text{-}N^3H\text{-}(CH_2)y\text{-}N^4(R_3)\text{-}R_4 \qquad (I)$$

wherein: $R_1$, $R_2$, $R_3$ and $R_4$ are the same or different and are H, alkyl, cycloalkyl or aralkyl having from 1 to 12 carbon atoms, or a heterocyclic group having from 3 to 10 atoms wherein the hetero atom is said $N^1$ or $N^4$;

Q is a cycloalkyl group having from 3 to 10 carbon atoms;

x is an integer from 3 to 6, inclusive;

and y is an integer from 3 to 6, inclusive;

or (II) a salt thereof with a pharmaceutically acceptable acid; and [B] a pharmaceutically acceptable carrier therefor.

2. The composition according to claim 1 wherein Q is connected either *cis* or *trans* as the (1,2), (1,3), (1,4), (1,5) or (1,6) isomer.

3. The composition according to claim 1 wherein Q is cyclohexyl.

4. The composition according to claim 1 wherein x is 3 and y is 3.

5. The composition according to claim 1 wherein x is 3, y is 3, $R_1$ and $R_3$ are both H and $R_2$ and $R_4$ are both ethyl.

6. The composition according to claim 1 wherein Q is cyclohexyl; x and y are 3; $R_1$ and $R_3$ are both H, and $R_2$ and $R_4$ are both ethyl.

7. The composition according to claim 6 wherein said polyamine is the *trans* (1,4) isomer.